REMARKS

Claims 1-12 are pending in the above-captioned application. Claims 2-6 and 10-12 are withdrawn. For instance, independent claim 1 is directed to an isolated nucleic acid have the sequence of SEQ ID NO: 1.

In the Office Action, the specification was objected to for various informalities. The above amendments to the specification answer these objections and present no New Matter to the specification as filed.

In the Office Action, claims 1 and 7-9 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

To satisfy the enablement requirement, a patent specification must describe the claimed invention in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains to make and use the same. The enablement requirement consists of two components. First, the specification must adequately describe how to make the invention. Second the specification must describe how to use the invention.

The USPTO carries the initial burden to establish a reasonable basis for questioning the enablement provided for the claimed invention. The enablement requirement is satisfied if the specification describes any method for making and using the claimed invention that bears a "reasonable correlation" to the entire scope of the claims. Moreover, while there must be some disclosure of specific starting materials or of the conditions for carrying out a process, the application need not contain within its four corners all of the information necessary to practice the claimed invention.

In the Office Action, it was correctly stated that the specification teaches SEQ ID NO: 1. The Office Action also mentions description found in the specification of *in vitro* treatment of cell lines via both the claimed sequence itself as well as the expression product of the sequence. For instance, in Example II, beginning at page 12, line 9, is described the full length of 8.31 (SEQ ID NO: 1) for use as a probe to examine its expression in NT2 cells. In addition, the Office Action states beginning at the last line of

page 5 that the specification suggests that 8.31 serves as a candidate marker for genetic disease. Thus, it would appear that the Office Action itself states that the specification describes at least one use for the claimed inventions.

A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

The claims presently under examination are product claims directed to an isolated nucleic acid (claim 1), a recombinant DNA construct (claims 7 and 8), and a cell transformed or transfected with a recombinant DNA construct (claim 9). The specification clearly describes to one of ordinary skill in the art how to make these products, as is required in U.S.C. §112, first paragraph (see, e.g., Example II, beginning at page 10, line 5). Thus, Applicants understand that the first component of the enablement requirement is clearly met.

Moreover, Applicants further submit that the second component of the enablement requirement, how to use the claimed products, has also been met. In particular, not only does the specification provide adequate description of *multiple* methods of using the claimed products, but additional methods would be well known to those of ordinary skill in the art, and thus are not described at length within the specification. For instance, in addition to the utilization of the claimed products for both *in vivo* and *in vitro* applications directed to HCC, the claimed products are also disclosed as being useful in, e.g., maintenance of the stem cell identity of progenitor cells, early differentiation of progenitor cells, embryogenesis, and proper functioning of the immune system (see, e.g., page 3, lines 21-27). One particular application of the materials of the claims under examination is in the diagnosis of hepatocellular carcinomas (HCC), and specifically the up/down-regulation of RAMP associated with

diagnosis of HCC, for instance via assays incorporating or developed through use of the claimed products. "Usefulness in patent law, and in particular the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this first becomes useful is well before it is ready to be administered to humans." (*In re Brana*, 51F.3d, 1560, 1568 34 USPQ2d 1436, 1442-43 (Fed. Cir. 1995.)

In the field of cancer biology, it is customary to identify one or more genes associated with a certain cancer with a view to diagnose and/or eventually treat that cancer once the gene(s) has or have been identified. Pre-diagnosis is considered an important element in a treatment regime because without a proper diagnosis or pre-diagnosis no specific treatment could be given. While identification of the gene(s) may be only a start in the whole picture of diagnosis and eventual treatment, a skilled person in the art would have no doubt in understanding that the identification is by far the most important and difficult step. In other words, once the gene(s) is/are identified, a definite diagnosis and eventual treatment is within reach. For this reason, biotechnology companies and pharmaceutical companies worldwide are racing each other and using all available methods seeking to identify the relevant gene(s) involved or associated with cancers. However, this initial exercise is neither easy nor predictable.

The connection or correlation of the presence, over-expression and/or under-expression of certain gene(s) and a cancer is a matter of degree. Scientifically speaking, it cannot be said with 100% certainty that once there is a certain level of correlation, a patient identified with that level of correlation must then have that cancer. However, there is a difference between a strong correlation and a weak correlation. At least in the medical field and especially in the field of cancer biology, once a high correlation has been established, realistically and practically that high correlation would be interpreted in a clinical sense to lead to a diagnosis of cancer.

As correctly noted in the Office Action, page 8 line 19 to page 9 line 8 of the specification notes that the over-expression of RAMP is indicative of HCC. More

specifically, over-expression of RAMP is detected in over 70% of patient samples with HCC (see, e.g., the last paragraph of page 8 of the application). In the field of cancer pathology, a correlation of at least 70% is considered a high correlation between gene expression and existence of an underlying pathology. For instance, Kondo, et al. (Clinical Cancer Research, Vol. 5, 4005-4012, December 1999, included with an Information Disclosure Statement filed herewith) is concerned with an increased expression of COX-2 in non-tumor liver tissue that is associated with shorter disease-free survival in patients with Hepatocellular carcinoma. Specifically, in the abstract of Kondo, et al. it as indicated, "...The level of Cox-2 increased from normal liver to chronic hepatitis to cirrhosis. The majority of cirrhotic livers (81%) displayed marked COX-2 expression. In dysplasias, COX-2 expression was mainly moderate or strong (88%). In HCC, 17% of samples displayed a high COX-2 expression, and 37% of samples expressed COX-2 at a moderate level. Concordant results were obtained with reverse transcription-PCR and Western blot analyses. Clinicopathological survey indicated a significant correlation between COX-2 expression and differentiated carcinoma (P = 0.019)...". At page 4009 in the Discussion section, it is indicated that "normal tissues devoid of viral infection showed little or no expression of COX-2, " (end of first paragraph of Discussion section) and "[i]t was of interest from a clinical point of view that an increase in the non-tumor tissues was significantly associated with relapse of HCC..." (final sentence, p. 4009). Kondo, et al. further reports that, "COX-2 expression in nontumor was closely related to the postoperative relapse of HCC. This aspect is of clinical importance because there is a possibility that pharmacological inhibition of COX-2 activity might improve patients' prognosis in the future..." (p. 4011, final paragraph of the Discussion section).

From Kondo, et al, it is apparent that the level of correlation or association required in the field of cancer biology to be indicative of a certain cancer would not even need to be as high as 70% as in the present application. An association of 88%, as in Kondo, et al., would certainly be considered as high and indicative of the cancer. Even

an association of 37%, also indicated in Kondo et al., would still be considered moderate in the indication. In particular, Kondo et al. describe that 17% of 46 HCC samples displayed a high COX-2 expression, and 37% of samples expressed COX-2 at a moderate level ($p<=0.0001$), indicating that approximately one-half of HCC samples expressed the COX-2 protein.

Determination of the genetic sequence for a specific expression product and the correlation of the expression of that product with a disease state such as a cancer is of primary importance in diagnosing and treating that disease state. Knowledge of a genetic sequence and expression product thereof, particularly when clearly correlated to disease as in the present disclosure, provide to the art a basis for any or all of recognition, treatment, monitoring, and prevention of disease.

The clinical value of the determination of the expression product of a specific gene sequence and the correlation of that information with a disease state cannot be overstated. This is well established throughout the art. For instance, according to Kariyama et al., 1999 (British Journal of Cancer, (1999) 81(8), 1080-1087, included in an Information Disclosure Statement filed herewith) the correlation of MAGE-1 and MAGE-3 expression to HCC was found to be 80% and 60%, respectively. Detection of these genes is useful in diagnosing early HCC. The results show the potential for peptides derived from MAGE-1 and MAGE-3 as potential immunotherapy targets for treating patients with HCC (Abstract).

Similarly, Clark et al. (British Journal of Cancer (1999) 81(6), 1002-1008, included in an Information Disclosure Statement filed herewith) discloses the presence of PIP mRNA in approximately 85% of primary breast tumors and 70% of nodal metastases (p. 1006, second column). This high degree of correlation of PIP mRNA expression in both primary breast tumors and nodal metastases demonstrates the PIP gene's usefulness as a potential marker for breast micrometastasis. Clark et al. further discloses the impact the PIP gene will have as a tumour marker in the clinical diagnosis of micrometastases (p. 1007, first column).

As can be gathered from these similar studies, a 70% association of the expression product encoded by the isolated nucleic acid of claim 1 with HCCs, as reported in the present application, is clinically indicative in terms of differentiating early HCCs from non-cancerous normal liver tissues. Products of the presently pending claims have been developed through recognition of the gene (or at least one of the genes) connected to HCC and provide, in one embodiment, methods of utilizing this gene in the context of diagnosis of HCC. As clearly described in the specification, normal liver tissues show very low or undetectable expression of RAMP, see, e.g., Fig. 8. The specification is thus clear in supporting the fact that there is indeed an association between the expression product of the claimed sequences and this particular disease.

With the claimed sequence and the indicative nature of the over-expression of the gene and the element level of RAMP available, there is provided in the pending application a milestone in prognosis of HCC, and such prognosis is a major element in any diagnosis, treatment and/or monitoring progress of treatment of disease. Only with the prognosis of disease such as HCC (for example as described in the present application), can suitable treatment be provided. For instance, treatment such as described by Kondo et al. (see page 4010, hepatectomy) could be preformed. In yet another use of the claimed products, patients suffering from HCC, having been treated accordingly, and after recovery, could then subsequently be monitored periodically via the claimed products with a view to determine the likelihood of any remission.

The most difficult step in understanding any type of cancer or diagnosis and/or treatment is the identification of the underlying gene. Once the underlying gene has been identified, as disclosed in the present application, the rest of the work, while it could be time-consuming in certain cases, would be straightforward. The presently claimed products are, in one particular embodiment, useful for diagnostic purposes of HCC, either as a positive basis for further diagnostic tests or as a starting point for early preventive therapy. A skilled person in the art would interpret the expression levels of

the expression product encoded by the isolated nucleic acid of claim 1 in samples taken from cancer patients and non-cancerous individuals as indicative. In particular, significant thresholds to determine a certain clinical diagnosis in a realistic perspective of developing HCC could be adapted to the reference sample population used. The p-value related to a marker association is preferably < 0.05, which is believed to be applicable to any association studies (see, e.g., Kondo et al., 1999; Kariyama et al., 1999; Clark et al., 1999). Further, a skilled person can use the range of values set forth above in performing association comparison with the expression of the expression product encoded by the isolated nucleic acid of claim 1 in a given individual. It would be understood by practitioners skilled in the treatment or diagnosis of HCC that the products of the present claims provide, in one embodiment, a method for indicating a risk level of developing HCC or indicate a response or side effect to treatment in a given individual. This information is extremely valuable as it contributes to a supplementary HCC diagnostic procedure and towards initiation of cancer treatment.

Additionally, even when considering methods of using the disclosed products that are directed to treatment of any one disease, such as HCC, it is to be noted that existing conventional techniques and procedures for engineering specific steps for diagnosis/treatment once an underlying gene is identified is well known in the art, and extended description of what is well known in the art need not, and preferably is not included in a patent application. Moreover, a skilled person in the field of cancer biology typically does not work in a vacuum as an individual but rather works in a team of scientists and oncologists and such individuals, particular when working as a team, would clearly see the claimed invention as enabled.

As to the specific cell lines described in the captioned application (e.g., NT2 cells, HL-60 cells), Applicants respectfully submit that it is commonly accepted practice in the field of the present invention to include human cell line samples during examination of the expression of a candidate genetic marker in human cancer tissues (see, e.g., Kondo et al., 1999; Kariyama et al., 1999; Clark et al., 1999). Such cell lines

are used with a view that they serve as a standard for the assay. In the field of the present invention, detailed mechanism of cancer development, such as disregulation of the cell cycle, can most successfully be studied with human cell lines as a model.

As a final matter, it should be understood that while the above discussion is primarily concerned with HCC, the pending claims are in no way intended to be limited to uses concerned with this particular disease state, and such application is only one of many applications encompassed by the pending product claims. As discussed above as well as discussed in the captioned application, the claimed products also find use in a plurality of other applications.

It is believed that the present application is in complete condition for allowance and favorable action, therefore, is respectfully requested. Examiner Harris is invited and encouraged to telephone the undersigned, however, should any issues remain after consideration of this response.

Please charge any additional fees required by this response to Deposit Account No. 04-1403.

Respectfully submitted,

DORITY & MANNING, P.A.

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Date

Christina L. Mangelsen, Patent Agent
Reg. No. 50,244
P.O. Box 1449
Greenville, SC 29602
(864) 271-1592
(864) 233-7342